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Iron therapy and cardiovascular disease

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Iron therapy and cardiovascular disease. Intensive iron therapy is now a generally accepted adjunct for the treatment of renal anemia with recombinant human erythropoietin. However, with the emerging role of iron in cardiovascular disease, carcinogenesis, infectious diseases, and other disorders, it is no longer appropriate to assume that any amount of stored iron is safe until proven otherwise. In this article, the history and current status of the "iron hypothesis" on ischemic heart disease are briefly reviewed, followed by comments on iron management practices for renal patients.

The hypothesis that iron depletion protects against ischemic heart disease was proposed in 1981 as an explanation for the striking sex difference in heart disease rates [1–4]. The virtual absence of myocardial infarction in menstruating women is associated with quite low levels of stored iron. Typically little or no excess iron is accumulated as long as regular monthly bleeding continues. Menstruating women continue to maintain the negligible levels of stored iron found in both men and women before age 20. Whole blood contains approximately 0.5 mg of iron per milliliter. Typical menstrual blood loss amounts to 30 to 60 ml per month, representing a loss of 180 to 360 mg of iron per year. When menstrual iron loss ceases for any reason, there is a prompt increase in the heart disease rate.

Men lack the menstrual iron leak and undergo a progressive accumulation rising rapidly with age from the low levels of adolescence. On the order of 1000 mg of sequestered iron is amassed by middle age. At age 45, men have roughly four times more iron in storage than women. An increasing incidence of myocardial infarction parallels the acquisition of stored iron starting two decades earlier in men than in women. The close parallels between rising heart disease rates and rising levels of stored iron at a young age in men and in later years in women prompted the suggestion that stored iron may have a central role in heart disease [1–4]. As women close the large stored iron gap with men, they progressively close the equally large difference in heart disease rates.

Key words: erythropoietin, ischemic heart disease, myocardial infarction, anemia.

The "iron hypothesis" has broad explanatory power [1–4]. Decreased levels of stored iron may be involved not only in the protection against myocardial infarction enjoyed by menstruating women, but also in the low heart disease rates seen among impoverished people in the world's poorer countries. In these populations, the age-dependent rise in stored iron is blunted by high-fiber diets that retard absorption of iron and by prevalent parasites that cause chronic blood loss from gut and bladder. Increased iron stores may have had a major role in the emergence of the present epidemic of myocardial infarction in developed nations early in this century. Improvements in public sanitation protected the population from iron-wasting gastrointestinal parasites, and increased consumption of meat assured a source of easily absorbable iron. Iron loss may be part of the explanation for lower disease rates associated with long-term regular aspirin use. Gastrointestinal microbleeding from daily use of aspirin can cause a cumulative loss of iron equal to that of typical menstrual iron losses.

The most important mechanisms by which iron depletion protects have not been defined, and unexpected modes of protection cannot be confidently ruled out. It is likely that iron depletion protects by more than one mechanism. The two leading candidates appear to be (*1*) a decrease in atherogenesis and (*2*) a decrease in myocardial injury following ischemic events.

It has been shown in experimental studies that iron overload enhances [5] and iron depletion decreases formation of atherosclerotic plaque [6]. Deliberate iron depletion in men increases the resistance of low-density lipoprotein to oxidation [7] and is associated with an increase in serum concentrations of high-density lipoprotein [8]. A recent study suggests that serum ferritin values over 50 ng/ml are associated with a marked increase in carotid atherosclerosis in men and in women [9].

A preponderance of evidence suggests that deferoxamine can protect heart muscle from reperfusion injury [2]. Hearts in these studies were taken from subjects who were not iron overloaded in any conventional sense. The data collectively support the possibility that only a very small burden of stored iron is required to promote heart muscle injury after an ischemic event. A given occlusive

event may or may not result in a clinically apparent infarction, depending on the burden of stored iron present.

Epidemiologic studies to date have not produced consensus on the role of iron in cardiovascular disease. Debate on the merits of the hypothesis has been muddied by several flawed negative studies [4]. A common flaw is that stored iron has been measured by inappropriate methods. A number of studies have used experimental designs that reflect an apparent misunderstanding of the iron hypothesis. In a 1994 editorial, Ascherio and Willett nonetheless acknowledged that the iron hypothesis cannot be rejected on the basis of available data: *"Stronger evidence is needed before the hypothesis is rejected that greater iron stores increase the incidence of coronary heart disease or death from myocardial infarction"* [10]. In other words, despite more than a decade of investigation and adversarial discussion, the hypothesis has not been invalidated. More recent studies confirm a major prediction of the hypothesis that volunteer blood donation is associated with a large and significant decrease in atherosclerosis and vascular events [9, 11, 12].

IRON THERAPY IN RENAL PATIENTS

In formulating strategies for avoiding anemia in renal patients, it appears to this observer that too little attention has been given to outcome, and too much has been devoted to achieving arbitrary hemoglobin targets. Potential hazards of stored iron have been largely ignored. These hazards may not be apparent in the short run. Failure to demonstrate cardiovascular toxicity in short-term studies with limited numbers of subjects does not assure that there is no myocardial injury [13]. "Free" plasma iron may cause myocardial injury. In the state of transferrin oversaturation, it must not be assumed that other ligands prevent the appearance of such free iron. There is a specific assay for free iron in plasma [14] that should be used to determine the concentration of free iron during intravenous iron therapy. It is likely that free iron regularly occurs in plasma during and following intravenous iron therapy. Cumulative damage to heart and other tissues cannot be ruled out on the basis of available evidence.

Chronic deleterious effects of stored iron overload are a concern beyond the issue of acute increases in free plasma iron. A key question concerns the definition of iron overload. Some have suggested that the serum ferritin must exceed 1000 ng/ml before iron overload occurs [15]. In my view, this is far too high. With this inadequate data base, medical judgement must play a dominant role in the formulation of guidelines. The case for using a ferritin value of 1000 ng/ml to define the threshold of iron overload is based on the lack of a consensus on specific hazards of serum ferritin at this level. However, there is also no convincing evidence that serum ferritin in this range is benign. It is clear that symptomatic hemochromatosis can be associated with serum ferritin values far below 1000 ng/ml at presentation. There are also experimental data that show increasing resistance to forms of oxygen-radical–mediated injury in iron-depleted subjects [16–20].

Iron overload should be defined as a clinical situation in which iron not needed or being used for erythropoiesis, that is, stored iron, contributes to a pathologic process. Iron overload cannot be excluded on the basis of measurements of iron in storage. It is not possible to assign a minimum cut-off value for stored iron or serum ferritin in the definition of iron overload. As noted earlier here, very small amounts of such iron may significantly promote myocardial injury after an ischemic event. In postischemic hearts, the stored iron burden, although small by conventional standards, is excessive in that it contributes to tissue pathology. Another example concerns chronic hepatitis C. Recent work suggests that removal of "normal" amounts of storage iron can often decrease the serum aminotransferase concentrations. Continued removal of iron from a patient with apparently total iron depletion can achieve additional decrements in aminotransferase levels [21]. In this situation, it has been suggested that aminotransferase levels be used instead of serum ferritin to assure that all of the overloading iron is removed. Chronic hepatitis is thus an example of iron overload from conventionally trivial amounts of storage iron.

The available data are not adequate to define precisely the relationship between net harm and level of iron overload. Neither the shape of the curve nor the x intercept is known with certainty. In other words, at what level of stored iron does net harm approach zero? The data do not rule out the possibility that stored iron may need to be reduced to zero to minimize harm. Clinical circumstances may alter the potential for harm from a given burden of stored iron. For example, a shift toward acid pH can release iron from transferrin, and a flux of superoxide ion, for example, from activated neutrophils, can free iron from its ferritin storage sites. The most conservative approach would be to place the burden of proof with those who maintain that any stored iron is safe.

The concept of functional iron deficiency needs to be systematically re-examined. Studies are needed of alternative ways of mobilizing endogenous iron stores during erythropoietin treatment. Perhaps simultaneous use of erythropoietin and deferoxamine would increase the mobilization of iron from its sequestered sites. The rate of stored iron removal by phlebotomy in hemochromatosis patients is highly variable. Stored iron in some sites is more resistant to mobilization and requires prolonged phlebotomy treatment and much patience on the part of physician and patient for complete removal. In patients with apparently unavailable stored iron, more pro-

longed erythropoietin therapy may free some of this iron for hematopoiesis. Studies on the addition of deferoxamine to the erythropoietin treatment regimen are needed.

Current practice in the use of iron during therapy with erythropoietin is based on a traditional view of iron toxicity. The conventional mind-set is that more or less any level of stored iron is benign as long as massive overload is avoided. This view largely ignores the potential hazards of stored iron, that is, iron in excess of needs. With the emerging role of iron in cardiovascular disease [1–4], carcinogenesis [22], infectious diseases [23], and other disorders [24], it is no longer appropriate to assume that any amount of stored iron is safe until proven otherwise. In my view, there is more support for the conclusion that stored iron is hazardous until proven otherwise.

NOTE ADDED IN PROOF

The findings of Besarab et al [1] suggest that treatment for raising hematocrit may in itself be hazardous for dialysis patients with heart disease. A spontaneously higher hematocrit appears to be beneficial. However, pushing a lower hematocrit value higher with epoetin and intravenous iron is associated with higher mortality. The most straightforward interpretation of these important findings is that the hematocrit level *per se* has less impact on the patient's outcome than the treatment used in achieving an arbitrary level. Unless renal physicians are willing to accept that epoetin itself is toxic, the most plausible explanation is that intravenous iron raises mortality in this setting.

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